



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Rima Kaddurah-Daouk *et al.*

Serial No.: 10/718,846

Filed: November 21, 2003

For: Use of Creatine or Creatine Analogs for the  
Treatment of Diseases of the Nervous System

Attorney Docket No.: AVZ-001CPUSCN

Group Art Unit: 1639

Examiner: Mark Shibuya

MS After Final  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**DECLARATION OF BELINDA TSAO NIVAGGIOLI, Ph.D.  
UNDER 37 CFR §1.132**

Dear Sir:

I, Belinda Tsao Nivaggioli, Ph.D., a citizen of Canada, residing in Atherton, California, hereby declare as follows:

1. I am presently the Chief Executive Officer of the Avicena Group, Inc. (Palo Alto, California). I have been working in the area of pharmaceuticals and nutraceuticals for approximately 14 years. A copy of my curriculum vitae is attached as Appendix A.

2. I have read the above-referenced application (included herewith as Appendix B) and presently pending claims 1, 2, 7, 8 and 13-16 (included herewith as Appendix C). It is my understanding that the invention is directed, at least in part, to a method for treating a subject afflicted with amyotrophic lateral sclerosis, by administering to the subject an amount of creatine or creatine phosphate, such that the subject is treated for amyotrophic lateral sclerosis.

4. In addition, I understand that claims 1, 2, 7 and 8 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Jennings (WO 094/17794), in view of Coffin (U.S.

5,492,930). In particular, the Examiner asserts that Jennings describes “compositions comprising amounts of creatine and creatine phosphate for use in treating wasting diseases.” Jennings describes the use of compositions comprising a sugar and a glycine derivative to enhance cardiac tissue formation. The Examiner relies on Coffin for teaching that “Alzheimer’s, as well as ALS, are members of a class of CNS neurodegenerative diseases with common etiology, (e.g., changes in excitatory amino acid transmission) and symptoms (e.g., reduced cognitive activity ability, e.g., dementia).”

5. Furthermore, I also understand that claims 1, 2, 7 and 8 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Jennings (WO 094/17794), in view of Flohe (U.S. 4,788,179). As described above, Jennings is directed to the use of compositions comprising a sugar and a glycine derivative to enhance tissue formation. Flohe is directed to the use of dipeptide compounds for the treatment of amyotrophic lateral sclerosis.

6. It is my opinion that the treatment of amyotrophic lateral sclerosis using creatine, as claimed in the present application, would not have been obvious over the cited references. In particular, creatine has been shown to have unexpected results in the treatment of amyotrophic lateral sclerosis.

7. In particular, two placebo-controlled randomized trials involving the administration of 5 grams of creatine per day to subjects suffering from amyotrophic lateral sclerosis were studied.

The two trials that were analyzed included a total of 211 patients, 103 creatine-treated and 108 placebo-treated patients. Although survival was not an endpoint in either trial, survival data was available for both.

For this analysis, a measure of treatment effect in an estimated pooled hazard ratio was calculated. This measure gives the risk of death for treated subjects divided by the risk of death for controls. Survival analysis by treatment was also performed for each trial separately. A Cox model was used to assess the hazard ratios and survival by treatment in the pooled data, controlling for trial effect and baseline variables. Baseline characteristics of the study populations were also compared. Continuous variables were compared by treatment and trial, using the analysis of variance by putting both treatment and trial as the dependent variables. A Cochran-Mantel-Haenszel test statistic was used

to compare discrete variables by treatment and trial, controlling for trial and treatment effects, respectively.

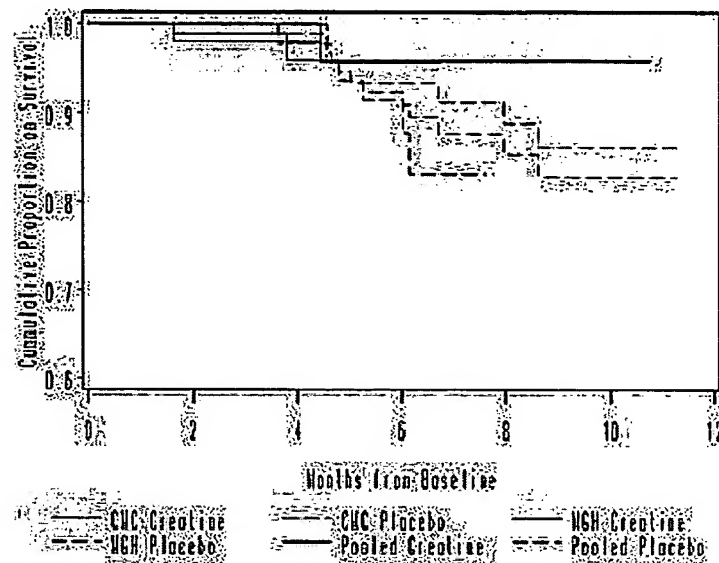
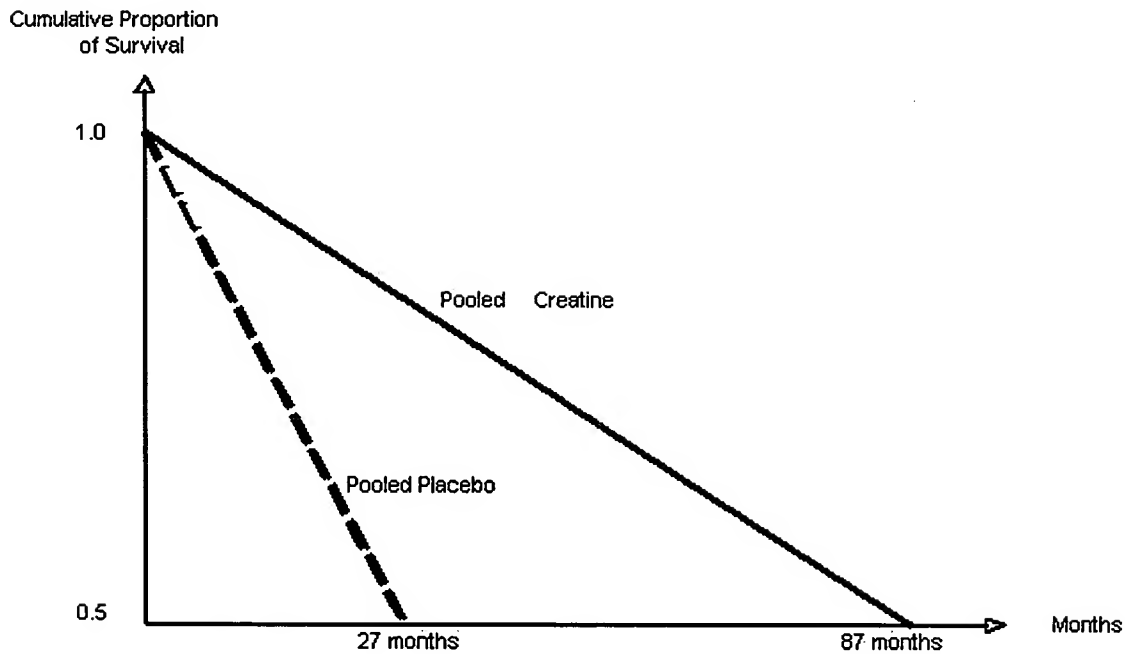


Figure 1

Five grams of creatine per day improved survival in the pooled data. The adjusted hazard ratio was 0.34 (95% confidence interval 0.11 to 1.04) for the creatine group relative to the placebo group. Median survival showed a two-to-three-fold improvement for subjects taking creatine over placebo (87 months compared to 27 months). The effect was homogeneous between trials ( $p=0.062$ , hazard ratio 0.34, 95% confidence interval 0.11 to 1.06), suggesting no major differences in survival due to subject variables. Figure 1 shows the survival analysis for each trial and pooled data. This analysis shows that creatine 5 grams daily prolongs median survival time in subjects with ALS.

Median survivals were also calculated. The median survival is the number of months 50% of the patients would have survived in each treatment arm. Since only a small percentage of patients died during the 8-11 month of study period, the median survival is statically calculated to project to the point where 50% of the patients would have died. Figure 2, below, shows that the median survival time of the subjects treated with creatine increased from 27 months to 87 months



**Figure 2**

8. It has been found that administering creatine to subjects suffering from amyotrophic lateral sclerosis extends the average survival time of the subjects fifty months (approximately four years). In contrast, treatment with Riluzole (the FDA approved amyotrophic lateral sclerosis drug) only extends average survival time approximately two to three months (Miller, R.G. *et al.*, Cochrane Database Syst Rev. 2002;(2):CD001447). For at least the above reasons, it is my opinion that creatine has surprising and unexpected therapeutic activity for the treatment of amyotrophic lateral sclerosis.

9. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.



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Belinda Tsao Nivaggioli, Ph.D.

June 13, 2007

Date

**Belinda Tsao Nivaggioli, Ph.D.**  
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**WORK EXPERIENCE****The Avicena Group, Inc., Palo Alto, CA**

Chief Executive Officer	1/05 - Present
Chief Operating Officer	12/01 – 1/05
Vice President of Operations	12/00 – 12/01
Director of Product Development	9/99 – 11/00

Avicena Group, Inc. (OTCBB: AVGO) is a late stage biotechnology company focused on developing products based on its proprietary understanding of the regulation of cellular energy processes. The company's core technologies, supported by a robust IP portfolio, have broad applications in both pharmaceuticals and dermaticals. Avicena's pharmaceutical program centers on rare neurological disorders (orphan diseases). The company is currently analyzing data from its Phase IIb/III trial in ALS (Amyotrophic Lateral Sclerosis, or Lou Gehrig's disease). Near term, Avicena intends to initiate a Phase III trial in Huntington's disease and a Phase III trial in Parkinson's disease. Avicena's science is well established and its products are safe and well tolerated. Unlike traditional biotechnology companies, Avicena's clinical programs are largely funded by government and non-profit organizations. Avicena presently derives revenue from the sale of proprietary ingredients to skin care manufacturers.

**Oral-B Laboratories, A Gillette Company, Belmont, CA**

Manager, Product Development, Floss and Interdental	11/98 – 9/99
Group Leader, Floss and Interdental	11/95 – 11/98

Development, scale up and manufacture of new interdental products, such as flosses and interdental devices. Involved in project management, procurement and setup of manufacturing line in the factory, market research, clinical studies, launch planning, preparation of sales materials and manufacturing logistics. Supervision of engineers and technicians.

**The Gillette Company, Boston, MA**

Research Scientist, Corporate Research and Development	11/94 - 11/95
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Synthesis and microbiological assays of novel antimicrobial agents for treating plaque and gingivitis. Synthesis and studies of acidochromic materials. Worked closely with various business units to develop strategic business plans. Supervision of technicians and students.

**Massachusetts Institute of Technology, Cambridge, MA**

	1993 - 1994
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Postdoctoral Associate in Prof. Julius Rebek Jr.'s group. Studied chemical nucleases, self-replicating systems and combinatorial libraries. Collaborated with Prof. Alan Hatton, in the Department of Chemical Engineering in the study of water-soluble polymers using NMR and fluorescence spectroscopy.

**EDUCATION****University of Toronto, Toronto, ON, Canada.**

*Ph.D. in Bioorganic Chemistry (January 1993).* Study of conformation catalysis of decarboxylation by host-guest chemistry. University of Toronto Open Fellowship (1990 - 1992).

*M.Sc. in Bioorganic/Physical Organic Chemistry (May 1990).* University of Toronto Open Fellowship (1988 - 1990).

**Oberlin College, Oberlin, OH, USA**

*A.B. (Hons) in Organic Chemistry (1988).* Li Shu Fan Foundation Scholarship (1984 - 1988).

#### **ASSOCIATIONS**

Member of American Chemical Society (ACS), American Association for the Advancement of Science, the Society of Plastics Engineers, International Association of Dental Research

#### **PUBLICATIONS / REFERENCES**

Available upon request. As of March 1998, 5 papers were published in international journals, 6 presented at international conferences, 1 patent granted and 2 patent applications are pending.

#### **LANGUAGES**

English, Chinese and French (proficient in reading, writing and conversation).

#### **HONORED MEMBERS**

Medicine's Who's Who 2004

**Pending Claims**  
U.S.S.N. 10/695,265

1. A method for treating a subject afflicted with amyotrophic lateral sclerosis, comprising administering to the subject an amount of creatine, such that the subject is treated for amyotrophic lateral sclerosis.
2. The method of claim 1, wherein said subject is a human.
7. A method for treating a subject afflicted with amyotrophic lateral sclerosis, comprising administering to the subject an amount of creatine phosphate, such that the subject is treated for amyotrophic lateral sclerosis.
8. The method of claim 7, wherein said subject is a human.
13. A method for reducing progression of amyotrophic lateral sclerosis in a subject, comprising administering to the subject an amount of creatine, such that the progression of amyotrophic lateral sclerosis in said subject is reduced.
14. The method of claim 13, wherein said subject is a human.
15. A method for reducing progression of amyotrophic lateral sclerosis in a subject, comprising administering to the subject an amount of creatine phosphate, such that the progression of amyotrophic lateral sclerosis in said subject is reduced.
16. The method of claim 15, wherein said subject is a human.